Efficacy and Safety of *Treximet* in the Treatment of Migraine for Patients Who Report Poor Response to Previous Short-Acting Triptan Use

This information is provided in response to your request for information about *Treximet*®(sumatriptan and naproxen sodium) Tablets. *Treximet* is a single-tablet formulation of sumatriptan 85 mg, formulated with RT Technology, and naproxen sodium 500 mg.

SUMMARY

- Two identical randomized, double-blind, placebo-controlled, crossover studies evaluated the efficacy of *Treximet* when treating migraine headaches in patients who had previously discontinued treatment with a short-acting triptan due to poor response or intolerance. In these studies, significantly more patients taking *Treximet* versus placebo achieved pain freedom over a period of 2 to 24 hours following treatment with *Treximet* without the use of rescue medication. In addition, significantly more patients treated with *Treximet* were pain-free at 2 hours following treatment compared with those who took placebo.
- *Treximet* was generally well-tolerated. Chest discomfort was the only adverse event reported by ≥2% of patients in the *Treximet* treatment group.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

TREATMENT OF MIGRAINE IN PATIENTS WHO REPORT POOR RESPONSE TO PREVIOUS SHORT-ACTING TRIPTAN USE: STUDY DESCRIPTION

The efficacy and tolerability of *Treximet* when treating migraine in patients who had previously discontinued treatment with a short-acting triptan due to poor response or intolerance were evaluated in two identical randomized, double-blind, placebo-controlled, crossover, two-attack studies.[1,2,3] Adult male or female patients were eligible for study inclusion if they met International Headache Society (IHS) criteria for migraine with or without aura and they recently (within 1 year) discontinued treatment with a short-acting triptan [rizatriptan (6-8% of patient population), sumatriptan (9-14% of patient population), almotriptan (4-5% of patient population), zolmitriptan (5-6% of patient population), and eletriptan (69-74% of patient population)] due to non-response, poor response, or intolerance. Hence, these patients represented a difficult-to-treat patient population. A poor responder was defined as a patient who had consulted with their physician prior to study entry and discontinued treatment with any of the aforementioned agents for reasons related to response, including (but not limited to): slow onset of efficacy, inconsistent efficacy, inadequate overall efficacy, or inadequate sustained efficacy through 24 hours. Intolerance was defined as discontinuation of treatment with a short-acting triptan for other reasons, attributable to the triptan, outside of non-response based on consultation with their physician. Patients were required to have 1-8 migraines per month over the last 3 months prior to screening.

A total of 173 and 169 patients were randomized in Study 106571 and Study 106573, respectively. Of those randomized, 139 patients in Study 106571 and 137 patients in Study 106573 comprised the intent-to-treat (ITT) population. Patients were instructed to treat two separate migraine attacks during the mild phase of each attack and within one hour of the onset of head pain in an early intervention paradigm. One attack was treated with one tablet of the *Treximet* and the other attack with one tablet of placebo (crossover design; randomized treatment order). A minimum 1-week washout period was

required between study medication treatment of the first and second migraine attacks. Rescue medication was permitted at 2 hours post-dose which may have been a single dose of sumatriptan, naproxen, an over-the-counter (OTC) pain-reliever, or an antiemetic. Medications not permitted as rescue within 24 hours after taking study medication were other non-naproxen long-acting nonsteroidal antiinflammatory drugs (NSAID), triptans (except sumatriptan), narcotics, or ergots. Other 5-HT agonists, analgesics containing morphine or codeine, a barbiturate or an opioid derivative, ergots, MAOIs, or long-acting NSAIDs were prohibited. Both studies evaluated *Treximet* against placebo for the proportion of patients who had sustained pain-free results from 2-24 hours post-dose (primary endpoint). Secondary endpoints included comparison of *Treximet* to placebo for the proportion of patients with pain-freedom at 2 hours post-dose; use of rescue medication; pain-freedom at 0.5, 1, 4, and 8 hours; migraine-freedom at 2, 4, 8, and 2-24 hours; recurrence of headache pain; migraine-associated symptom (photophobia, phonophobia, nausea) freedom at 2, 4, 8, and 2-24 hours; any migraine symptom (migraine-free and neck and sinus pain-free) freedom at 2, 4, 8, and 2-24 hours; and safety and tolerability.

TREATMENT OF MIGRAINE IN PATIENTS WHO REPORT POOR RESPONSE TO PREVIOUS SHORT-ACTING TRIPTAN USE: EFFICACY

Efficacy results are presented in Table 1

Table 1. Efficacy of *Treximet* for the Treatment of Migraine in Patients who Report Poor Response to Previous Short-Acting Triptan Use – Intent To Treat (ITT) Population[1,2,3]

	Study 106571		**Study 106573**	
	Treximet **(n=136)**	**Placebo (n=134)**	***Treximet*** **(n=134)**	**Placebo (n=133)**
Sustained pain-free from 2-24 hours post-dose (primary endpoint) [OR (CI)]	26% [4.50 (2.17, 9.36)]*	8%	31% [5.63 (2.76, 11.49)]*	8%
Pain-free for 2 hours post-dose (key secondary endpoint) [OR (CI)]	40% [3.19 (1.80, 5.65)]*	17%	44% [4.69 (2.57, 8.55)]*	14%
Rescue medication use [OR (CI)]	29% [0.24 (0.16, 0.38)]*	63%	22% [0.22 (0.14, 0.37)]*	55%
Pain-Freedom[OR (CI)]				
0.5 hours	4% [2.91 (0.57, 14.95)]	2%	2% [1.00 (0.20, 5.07)]	2%
1 hour	19% [2.20 (1.05, 4.59)]†	10%	25% [3.19 (1.60, 6.38)]‡	9%
4 hours	59% [4.93 (2.85, 8.54)]*	23%	62% [8.11 (4.37 , 15.03)]*	17%
8 hours	65% [5.81 (3.38, 9.98)]*	24%	66% [6.20 (3.58, 10.76)]*	24%
Migraine-Free [OR (CI)]				
2-24 hour post-dose	24% [3.43 (1.63, 7.20)]‡	8%	25% [5.45 (2.52, 11.80)]*	6%
2 hour migraine-free	35% [3.18 (1.75, 5.76)]*	14%	35% [4.14 (2.20, 7.80)]*	11%
4 hour migraine-free	53% [3.88 (2.28, 6.61)]*	23%	57% [7.85 (4.17, 14.77)]*	15%
OR=Odds Ratio; CI=95% confidence interval for odds ratio; *$P<0.001$ vs. placebo; † $P<0.05$ vs. placebo; ‡ $P=0.001$ vs. placebo;				

	Study 106571		Study 106573	
	Treximet **(n=136)**	**Placebo (n=134)**	***Treximet*** **(n=134)**	**Placebo (n=133)**
8 hour migraine-free	59% [5.14 (2.99, 8.89)]*	22%	63% [5.97 (3.42, 10.39)]*	23%
Any Migraine-Associated Symptom Freedom (Migraine-Free and Neck and Sinus Pain-Free) [OR (CI)]				
2-24 hour post-dose	22% [3.95 (1.79, 8.72)]‡	7%	22% [5.50 (2.43, 12.43)]*	5%
2 hours	32% [0.28 (0.15, 0.52)]*	12%	29% [0.21 (0.11, 0.42)]*	8%
4 hours	46% [0.28 (0.17, 0.47)]*	20%	47% [0.17 (0.09, 0.32)]*	14%
8 hours	54% [0.21 (0.12, 0.36)]*	20%	56% [0.18 (0.10, 0.32)]*	20%
OR=Odds Ratio; CI=95% confidence interval for odds ratio; *P<0.001 vs. placebo; † P<0.05 vs. placebo; ‡ P=0.001 vs. placebo;				

Other secondary endpoints included the associated symptoms of migraine; photophobia, phonophobia, and nausea.*Treximet* provided significantly more patients freedom from photophobia and phonophobia at 2, 4, 8, and 2-24 hours. *Treximet* also provided significantly more patients freedom from nausea at 4 (Study 106573 only), 8, and 2-24 hours.

TREATMENT OF MIGRAINE IN PATIENTS WHO REPORT POOR RESPONSE TO PREVIOUS SHORT-ACTING TRIPTAN USE: SAFETY

In these studies 11% and 9% of patients who took *Treximet* (Studies 106571 and 106573, respectively) and 4% and 5% of patients who took placebo (Studies 106571 and 106573, respectively) experienced an adverse effect.[1,2,3] Drug-related adverse events occurred in 8% of patients who took *Treximet* in Study 106571, compared with 1% who took placebo, and in 7% of patients who took *Treximet* in Study 106573 versus 4% in the placebo group. The only adverse event that occurred at an incidence of ≥ 2% in any study group was chest discomfort in the group who received *Treximet* (Study 106571). Most adverse events were reported as mild or moderate in severity, and no serious adverse events were reported in either study.

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

1. Data on File. Study 106571, 2008. *
2. Data on File. Study 106573, 2008. *
3. Mathew NT, Landy S, Stark S, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. Headache 2009;doi: 10.1111/j.1526-4610.2009.01458.x (online).*